DERMATOLOGICA SINICA 31 (2013) 154–156

Contents lists available at SciVerse ScienceDirect

Dermatologica Sinica

journal homepage: http://www.derm-sinica.com

CASE REPORT

Tegafur/gimeracil/oteracil (TS-1) induced Stevens–Johnson syndrome: Case report

Satoko Minakawa*, Yasushi Matsuzaki, Koji Nakajima, Hajime Nakano, Daisuke Sawamura

Department of Dermatology, Hirosaki University, School of Medicine, Japan

ARTICLE INFO

Article history:
Received: Aug 27, 2012
Revised: Dec 26, 2012
Accepted: Dec 27, 2012

Keywords:
drug eruption
gimeracil
oteracil
Stevens–Johnson syndrome
tegafur
TS-1

ABSTRACT

TS-1 is an oral fluoropyrimidine anticancer drug that contains tegafur, gimeracil, and oteracil. A 78-year-old Japanese male who was diagnosed with carcinoma of the oral floor (rT4aN0M0) was prescribed a standard dose of TS-1 (80 mg/day). On Day 8 after administration of TS-1, an eruption developed. There was erythema, along with vesicles and erosions involving the lip, face, neck, trunk, limbs, and genitals. The drug-induced lymphocyte stimulation test (DLST) for TS-1 was negative on the 23rd day, but positive on the 43rd day (20 days after discontinuing prednisolone). The condition was diagnosed as Stevens–Johnson syndrome due to TS-1 because of the clinical course and laboratory results. This case and 24 cases previously reported in the literature were analyzed. The types of drug eruption were drug-related lupus (9 cases), acral erythema (7 cases), scleroderma-like skin lesion (2 cases), Stevens–Johnson syndrome (2 cases), lichenoid eruption (1 case), purpura (1 case), lichen planus (1 case), erythema multiforme (1 case), hypopigmentation (1 case) and toxic epidermal necrolysis (1 case), respectively. In view of the increasing usage of TS-1 in several common cancers, clinicians should be aware of drug eruptions due to TS-1.

Introduction

TS-1 is an oral fluoropyrimidine anticancer drug that contains tegafur [a prodrug that cells metabolize to fluorouracil (FU)], gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades FU), and oteracil (which inhibits the phosphorylation of FU in the gastrointestinal tract, thus reducing its side effects on the gastrointestinal tract).[1] We describe the case of a patient who developed a rare complication of Stevens–Johnson syndrome (SJS) 8 days after adjuvant TS-1 administration. To clarify the clinical characteristics of drug eruption associated with TS-1, this case and 24 previous cases reported in the literature were analyzed.

Case report

A 78-year-old Japanese man who was diagnosed with carcinoma of the oral floor (rT4aN0M0) was prescribed a standard dose of tegafur/gimeracil/oteracil (TS-1) at 80 mg/day. On the Day 8 after TS-1 administration, he developed eruptions on his axillae. On the 10th day, TS-1 was discontinued because of worsening of the confluent erythema involving the body, blisters on his genitals, and erosions associated with left eye tearing. Therefore, he was treated with 30 mg of prednisolone (PSL). On the 15th day, he developed fever. He also experienced diarrhea that could not be controlled with antidiarrheal medication. On the 18th day, he was referred to our department.

On physical examination, erythema, vesicle formation, and erosions involving the lip, face, neck, trunk, limbs, and genitals were observed (Figure 1). His laboratory investigation results on admission were as follows: white blood cell count, 1.246×10^9/L; absolute neutrophil count, 81.7%; eosinophil count, 0%; hemoglobin level, 110 g/L; and platelet count, 232×10^9/L. Levels of antinuclear antibody, ds-DNA, and anti-BP180 antibody were within normal ranges. Nikolsky's sign was negative. Ophthalmological evaluation did not reveal any eye involvement. A skin biopsy specimen taken from his right thigh showed slight hyperkeratosis, many necrotic keratinocytes in the epidermis, subepidermal bulla formation, and vacuolar degeneration of the basal layer with infiltrations mainly comprising lymphocytes and eosinophils. In addition, lymphocytes and eosinophils had infiltrated the vessels of the superficial dermis (Figure 2).

On the 23rd day, the eruption was improved and therefore we discontinued oral PSL. The drug-induced lymphocyte stimulation test (DLST) performed at that point was negative for TS-1 (stimulation index, 162%). On the 43rd day (20 days after discontinuing PSL), the results of closed patch tests performed using 50%, 25%, and 12.5% TS-1 on the lesional area were negative, but the DLST result

* Corresponding author. 5 Zaifu-cho, Hirosaki 036-8562, Japan. Tel.: +81 172 39 5087; fax: +81 172 37 6060.
E-mail address: minakawas@yahoo.co.jp (S. Minakawa).

1027-8117/$ – see front matter
http://dx.doi.org/10.1016/j.dsi.2012.12.005

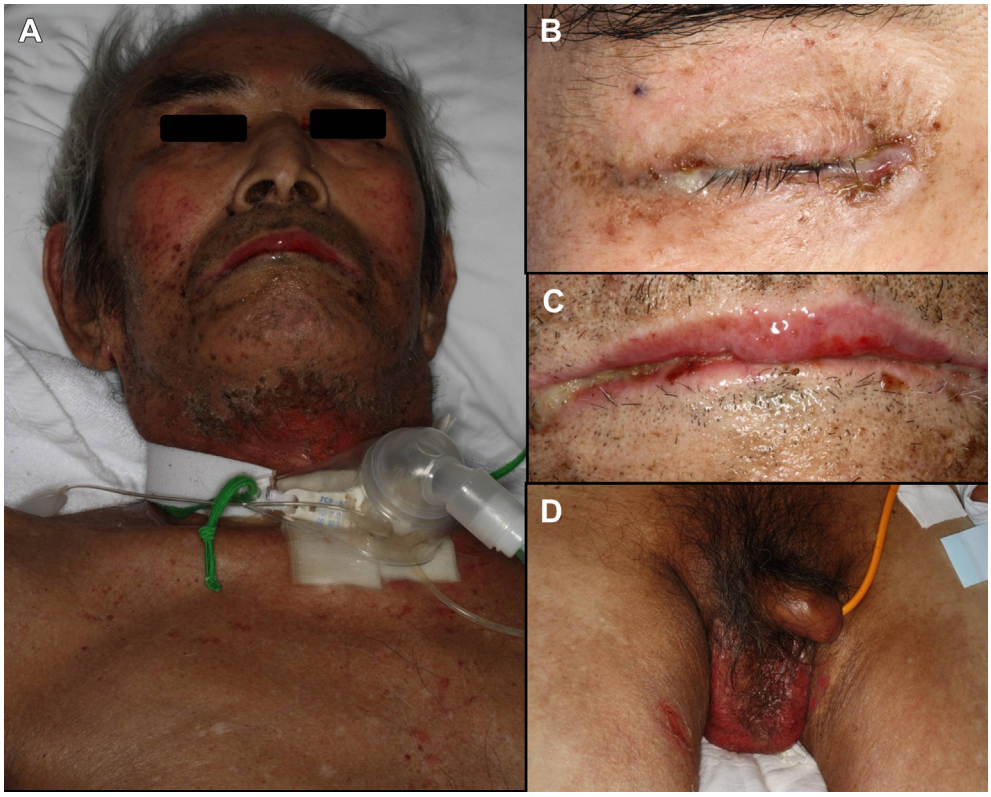

Figure 1 (A–D) A 78-year-old man with erythema, vesicle formation, and erosions involving the lip, face, neck, trunk, limbs, and genitals.

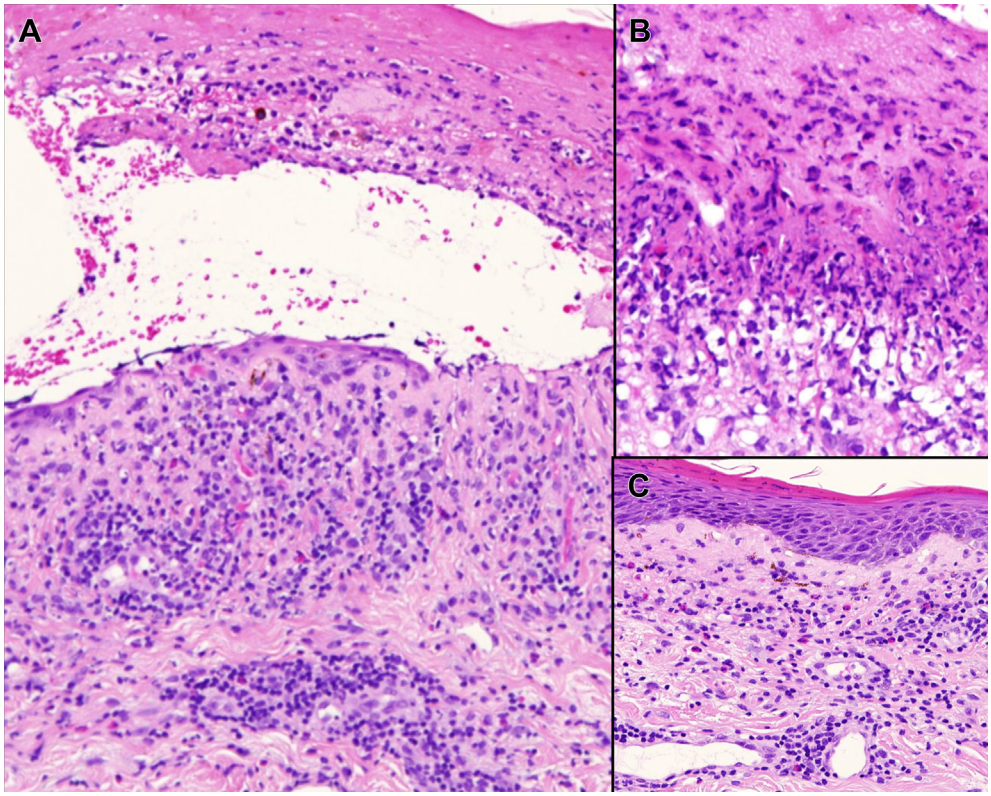

Figure 2 (A) A skin biopsy specimen showed subepidermal bulla formation and vacuolar degeneration of the basal layer with infiltrations mainly comprising lymphocytes and eosinocytes. (B) Many necrotic keratinocytes were found in the epidermis, and (C) lymphocytes and eosinocytes infiltrated the vessels of the superficial dermis.

Table 1 Review of the drug eruptions due to TS-1.

Patient	Sex	Age (y)	Type of eruption	Duration of therapy	Examination	Reference
1	F	31	Drug-related lupus	21 d	Administered+ ; ANA+; anti-ds–DNA+	2
7	M	63	Drug-related lupus	10 d		2
8	F	51	Drug-related lupus			3
12	F	48	Drug-related lupus		Administered+	3
13	M	72	Drug-related lupus	84 d	DLST–; PT–	3
15	M	64	Drug-related lupus	20 d	DLST–	3
17	M	67	Drug-related lupus	14 d	Anti-SS–A/R0+; DLST–; PT–	3
22	F	69	Drug-related lupus			4
14	M	62	Drug-related lupus and acral erythema	6 mo	Anti-SS–A/R0+	3
2	M	68	Acral erythema and hyperpigmentation	4 mo	DLST+; PT–; Administered+	2
3	M	62	Acral erythema and hyperpigmentation	12 d		2
4	M	73	Acral erythema and hyperpigmentation	17 d	Administered+	2
18	F	64	Acral erythema and hyperpigmentation	160 d		2
19	M	68	Acral erythema and hyperpigmentation	25 d		2
20	F	47	Acral erythema and hyperpigmentation	28 d		2
5	M	63	Scleroderma-like eruption	16 mo		3
10	M	81	Scleroderma-like eruption	10 d		3
9	F	71	Stevens–Johnson syndrome	21 d	Administered+	3
25	M	78	Stevens–Johnson syndrome	8 d	DLST+; PT–	Our case
6	M	66	Lichenoid eruption	10 d		2
11	M	74	Purpura	24 d	Administered+; PT–	2
16	M	72	Lichen planus	14 mo		3
21	M	72	Erythema multiforme	8 d		2
23	M	65	Hypopigmentation	6 mo	ANA+	5
24	F	64	Toxic epidermal necrolysis	28 d		1

was positive (stimulation index, 366%). We diagnosed the condition as TS-1-associated. SJS was diagnosed on the basis of the clinical course and laboratory results.

Discussion

A total of 25 cases involving TS-1-associated drug eruptions were analyzed[1–5] (Table 1). Levels of antinuclear antibody were positive in Cases 1 and 23. The results of patch tests were negative in Cases 2, 11, 13, 17, and our case. The DLST results were positive in Case 2 and our case, but the results were negative in Cases 13, 15, and 17. The results of drug challenge test were positive in Cases 1, 4, 9, 11, and 12.

In patients who are suspected to develop allergic reactions, DLST involving the incorporation of [^{3}H]thymidine ratio into the DNA of lymphocytes derived from patients, is generally employed for identifying drugs that could induce allergy. However, DLST results may show a false-negative response because of steroid, antitumor, and immunosuppressive drugs. Immediately after the onset of drug allergies, patients are also thought to be more susceptible to false-negative reactions. In view of the occurrence of false-negative results, the possibility of drug-induced allergy in patients receiving TS-1 should be carefully evaluated using a combination of other clinical examinations.

Common features of drug-related lupus are as follows: rare cutaneous manifestations, a high incidence of antihistone antibodies, and reversible symptoms after withdrawal of offending agents.[6] The frequency of discoid lupus erythematosus-like eruption is about 10% among all cases of drug eruptions induced by FU, based on the statistical report of Fukuda,[3] but the finding is the proportion of drug-related lupus (9 of 24; 37.5%) in this study. Basal cells are the target cells most affected by FU agents, because they are stem cells and are multipotent. Therefore, basal cells damaged by FU agents seem to be highly susceptible to ultraviolet light (UVL) irradiation, which induces liquefaction changes and patchy lymphocytic infiltrations.[6] Drug-related lupus by FU agent may be an excellent model for understanding the pathomechanisms of development of discoid lesions.[6]

Bleomycin and cisplatin are known to induce systemic sclerosis-like reactions in a genetically susceptible host.[7] Similarly, toxic effects or immune system modulation by the FU might be responsible for systemic sclerosis-like reactions.

FU exerts its antitumor effects through several mechanisms, including inhibition of RNA synthesis and function, inhibition of thymidylate synthase activity, and incorporation into DNA, leading to DNA strand breaks.[8] When FU is orally administered, extensive first-pass metabolism of FU in the gastrointestinal wall and liver decreases FU plasma levels and causes severe intestinal mucosal damage.[8] The potent inhibition of dihydropyrimidine dehydrogenase by gimeracil present in TS-1 may expose the patient to a high level of active FU metabolite. This may induce a high incidence of drug eruption.

To the best of our knowledge, this is the first review of the literature associated with TS-1. In view of the increasing usage of TS-1 in several common cancers, clinicians should be aware of drug eruptions associated with TS-1 administration.

Acknowledgments

This work was supported in part by Grants-in-Aid from the Ministry of Education, Science, Sports, and Culture of Japan (project 24791131, to S. Minakawa), and by the 2012 Hirosaki University Research Support System.

References

1. Tan CS, Lim R, Lim TC, Aw CW, Yeo SW, Lee SC. Toxic epidermal necrolysis associated with TS-1 in a patient with gastric cancer. *Jpn J Clin Oncol* 2011;**41**:666–8.
2. Kitagawa C, Yamada Y, Yoshida I, et al. Tegafur, gimeracil, oteracil potassium induced purpuric drug eruption. *Rinsyo derma (Tokyo)* 2009;**51**:1857–61 [Article in Japanese].
3. Fukuda E. *Collected report of drug eruption in Japan*. 13th ed. Shime Town: Fukuda Dermatology Clinic; 2010. pp. 300–301, [Article in Japanese].
4. Anzai S, Akashi Y, Tada K, et al. Two cases of drug eruption. *Nishinihon J Dermatol* 2011;**73**:102 [Article in Japanese].
5. Hyodo I, Ota M, Kobayashi A. A case of hypopigmentation triggered by S-1. *Gan To Kagaku Ryoho* 2009;**36**:875–7 [Article in Japanese].
6. Yoshimatsu T, Hiroi A, Ueda K, Furukawa F. Scleroderma-like reaction induced by uracil-tegafur (UFT), a second-generation anticancer agent. *Eur J Dermatol* 2001;**11**:54–7.
7. Kono T, Ishii M, Negoro N, Taniguchi S. Discoid lupus erythematosus (DLE)-like lesion induced by uracil-tegafur (UFT). *J Am Acad Dermatol* 2000;**42**:519–20.
8. Kobayakawa M, Kojima Y. Tegafur/gimeracil/oteracil (S-1) approved for the treatment of advanced gastric cancer in adults when given in combination with cisplatin: a review comparing it with other fluoropyrimidine-based therapies. *Onco Targets Ther* 2011;**4**:193–201.